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Incidence and prevalence of recognised and unrecognised myocardial infarction in women

The Reykjavik Study

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Aims The incidence and prevalence of recognised and unrecognised myocardial infarction were determined in the Icelandic cohort study of 13 000 women (the Reykjavik Study), followed for up to 29 years (mean 15 years).

Methods and Results Women attending the Reykjavik Study, born between 1908 and 1935, were examined in five stages from 1968 to 1991. A health survey included history and ECG manifestations of coronary heart disease. Data retrieved from hospitals, autopsy records and death certificates identified 596 fatal and non-fatal myocardial infarctions to the end of 1992 (61 prior to examination, 320 non-fatal and 215 fatal). The incidence of recognised myocardial infarction ranged from 22 cases/100 000/year at 35–39 years to 1800 cases/100 000/year at 75–79 years. The incidence of unrecognised myocardial infarction ranged from 18 cases/100 000/year at 35 years to 219 cases/100 000/year at 75 years. Thirty-three percent of non-fatal myocardial infarctions were unrecognised. More occurred in the younger age groups (40%) than in the older (27%). The prevalence of recognised myocardial infarction was influenced by age and calendar year. In 1990, it was 1·3/1000 at 35 years and 60/1000 at 75 years. Prevalence showed a time trend, tripling in all age groups from 1968–1992. For unrecognised myocardial infarction, prevalence rose from 0·9/1000 at 35 years to 19·2/1000 at 75 years, although there was no evident time trend.

Conclusion Myocardial infarction in women is very age-dependent, with both incidence and prevalence increasing continuously and steeply with age. There was a significant trend for an increase in prevalence of recognised myocardial infarction from 1968 to 1992. The proportion of unrecognised non-fatal infarctions ranged from 27% in the oldest age group to 40% in the youngest. On average, this form of coronary heart disease is as common as in men.
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Key Words: Coronary heart disease, myocardial infarction, women, population survey, prevalence, incidence, trend, unrecognised myocardial infarction, epidemiology.

See page 980 for the Editorial comment on this article

Introduction

In recent years there has been increasing attention on coronary heart disease as an important cause of mortality and morbidity among women. In 1987, a workshop under the auspices of the National Institutes of Health, concluded that there was insufficient data from developed countries[1]. Many epidemiological studies on the prevalence of coronary heart disease are based on self-reporting by participants[2]. Although the prognostic importance of unrecognised myocardial infarction is widely acknowledged[3–5], very few studies have addressed this form of disease among women.

The Reykjavik Study, initiated in 1967, is a population survey with a total of 31 000 participants, approximately 15 000 men and 16 000 women. Recent publications have described the prevalence and long-term prognosis of various forms of coronary heart disease in men[3–5].

The objectives of this study were to determine the prevalence and incidence of recognised and unrecognised myocardial infarction among women in Iceland, and trends over time from 1968 to 1992. Our method is a longitudinal survey utilizing self-reporting of disease, ECGs obtained during study visits and retrospective disease verification.

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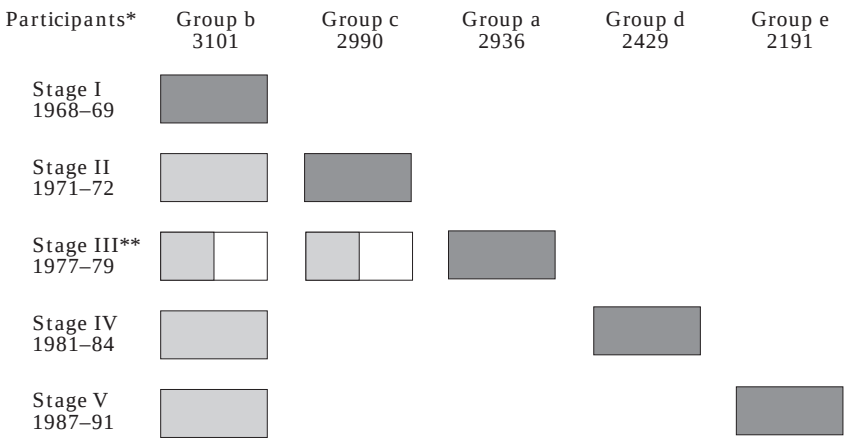


Figure 1 **Health survey stages in women from the Reykjavik Study. *Participants are all those selected for participation in 1966; those examined are referred to as attenders. **In stage III, only half of the women were invited from groups b and c[6]. Darker tints indicate baseline invitations, lighter tints repeated invitations of part of the cohort.**

Subjects and methods

The Reykjavik Study, initiated in 1967, is a prospective cardiovascular population study that included participants from the capital city, Reykjavik, and communities adjacent to it. In 1968, the area was inhabited by about 104 000 persons, close to half of the total population of Iceland at that time.

The study cohort (31 000 participants) was divided into six groups. Five groups formed the first five stages of the health survey now completed (Fig. 1). The women selected to participate were invited to a two-visit examination. The mode of invitation and physical examination has been described in detail[6] and comprised a thorough questionnaire, which included the Rose chest pain questionnaire[7], laboratory investigations, ECG, chest X-ray in two planes and spirometry. The 12-lead resting ECG was evaluated according to the Minnesota code[8].

The female participants were selected from the National Roster, a computerized continuously updated population register established in 1953, based on a compulsory lifetime personal identity number. The women chosen were born in 1908–1935 and were residing in the study area, on 1 December 1966. The groups a, b, c, d, e and f were constructed by stratified sampling on day and year of birth. Group f was not invited to the first five stages of the survey.

Identification of coronary heart disease in cohort

To identify and validate myocardial infarctions among female attenders, all available hospital records for all attenders (irrespective of disease status) from 1968 to the end of 1992 were reviewed. Additionally, records of any hospitalizations before the first visit (in 1968) were reviewed for those with history of heart disease. Subjects of this search were those attending the clinic at any one time, a total of 9773 women, ranging in age from 33 (in 1968) to 83 years (in 1992).

The data search was in three main parts:
(1) Identifying women who died from coronary heart disease (death certificates and autopsy records).
(2) Examining hospital files for women with a previous history of hospitalization for heart disease (i.e. before 1968 or their first visit).
(3) Searching hospital records in the Reykjavik area for hospitalizations after the first visit, and obtaining information from general practitioners throughout the country on women living in other parts of the country.

The data were culled from hand-written registers and record-linked registries as appropriate. In this way we identified women who had been hospitalized and discharged with an ICD diagnosis of 410–414·9 (ICD9), or corresponding numbers in ICD7 and ICD8[9]. Registered admissions were 1536 (1320 computerized), 1496 records were available (97%) and examined by one person (L.S.J.) over a 2-year period from 1992 to 1994. Data were added from the MONICA registry of coronary events in Iceland, as applicable.

MONICA criteria were chosen as the diagnostic protocol for myocardial infarction, with the case registry extended to all ages. ECG coding was according to the Minnesota code[10]. The following criteria for recognised and unrecognised myocardial infarction were applied:
(1) Recognised myocardial infarction: women were classified as having suffered a recognised (symptomatic) myocardial infarction if hospital records fulfilled the MONICA criteria for definite/possible myocardial infarction[10]. (The criteria are: (a) definite ECG changes (Minnesota codes 1:1:1–1:2:5 and 1:2:7) and (b) symptoms typical or atypical or inadequately described, together with probable ECG changes and abnormal enzymes (elevation $\geq$ double the laboratory's 'normal

Table 1 Attendance and response rate of women in the Reykjavik Study

	Year	Invited	Attended	Attended first time	Response rate*	Adjusted** response rate
Stage I	1968–1969	3090	2371	2371	76·7%	76·9%
Stage II	1971–1972	5998	4184	2306	69·8%	70·1%
Stage III	1977–1979	5771	3902	2086	67·6%	68·1%
Stage IV	1981–1984	5145	3587	1702	69·7%	70·4%
Stage V	1987–1991	4647	3029	1308	65·2%	67·7%

*Those who had died or emigrated at the beginning of each stage were subtracted from the total group before attendance was calculated.
**Adjusted response rate refers to the number of women who were alive at the midpoint of each stage. This adjustment was carried out to illustrate the effect of women, especially at later stages, who had died before they could be invited to participate.

values') or (c) symptoms typical and abnormal enzymes with ischaemic or non-codable ECG.)
(2) Unrecognised myocardial infarction: prevalence was determined if the ECG from the first visit showed signs of myocardial infarction, but without a history of clinical recognition. Incidence was determined from both visits, with women showing no signs of myocardial infarction on the ECG on the first visit, but presenting a definite ECG finding of an infarction (Minnesota codes 1:1:1–1:2:5 and 1:2:7) on a second visit, with no symptoms leading to clinical recognition of the event.

Quality control

From the outset of the study, the same personnel have administered the questionnaires, and the same physician (N.S.) has read and coded the ECGs independent of previous diagnoses. The World Health Organisation Reference Centre for ECG-coding at the Hungarian Institute of Cardiology in Budapest was used to monitor quality control of ECG coding. Accuracy of the case registration was evaluated by comparing diagnoses for 104 cases, previously reviewed by the MONICA recording team in Iceland. There was a 90% agreement in diagnostic categories (diagnostic categories agreed in 82% of cases, while in 8% the category changed from a definite event to a possible event or vice versa).

Statistics

Logistic regression was applied to evaluate the prevalence of myocardial infarction, as a function of age and calendar year, to the results of the first visit of each woman who attended. For computation of incidence of recognised myocardial infarction, Poisson regression was used. The incidence of recognised myocardial infarction was computed using all persons without symptomatic infarction at the first visit and their available risk period up to 5 years. To compute incidence of unrecognised myocardial infarction, consecutive visits were paired and each pair was used. Pairs were excluded if myocardial infarction was diagnosed during the former visit. The risk period was the time elapsed between two visits (2·2 to 9·7) and age was the subject's age halfway between visits. Significance testing was two-sided and based on a 5% probability level. Thus, results are presented with 95% confidence intervals. The software package used was SPIDA[11].

Results

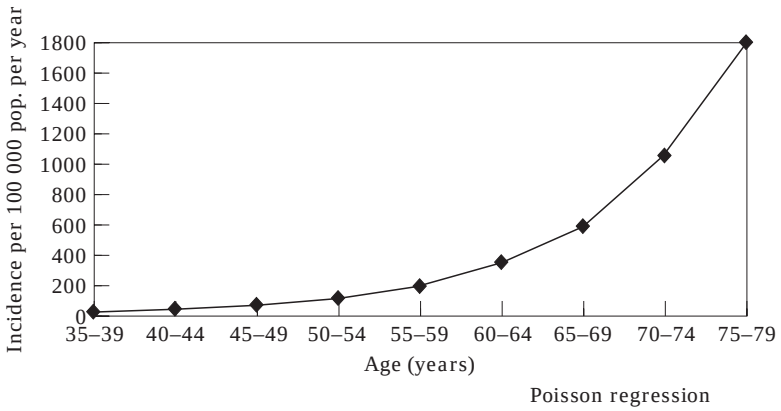
A total of 9773 women attended at least once in the first five stages of the Reykjavik Study. Women in group b were invited to every stage of the study (half of group b in stage III) and those in group c were invited to stages II and III (half of group c in stage III)[6]. By 31 December 1992, 1301 of the women had died. Seventy-two percent of the women from the original cohort had attended (Table 1). The autopsy rate for 1968–1985 was 53% for total mortality and 47% for coronary heart disease mortality (ICD9 410–414). After 1985, the autopsy rates according to the MONICA registry for ages 45–74, decreased to 38%, while remaining somewhat higher (46%) in the youngest age groups. During the study period, the census of all those attending has been updated, and 49 attenders (0·5%) are lost to follow-up, having moved abroad. At the end of the study period, 369 women or 3·8% had moved to other parts of the country. Retrieval of recorded admissions due to coronary heart disease was 97%, with missing records distributed over the study period.

Prevalent cases of myocardial infarction at first examination were 106, of which 45 were clinically unrecognised (Table 2). Total numbers of identified cases of myocardial infarction after the first examination (in the follow-up period) were 535, of which 215 were fatal.

The incidence of recognised myocardial infarction was age dependent and increased from 22 cases per 100 000 per year at ages 35–39 to 1800 cases per 100 000 per year at ages 75–79. The incidence of recognised infarction approximately tripled every 10 years of age (Fig. 2). The incidence also increased with age for unrecognised events (Poisson regression, $P = 0{\cdot}02$) ranging from 18 cases per 100 000 per year at age 35, to 219 cases per 100 000 per year at age 75 (Fig. 3).

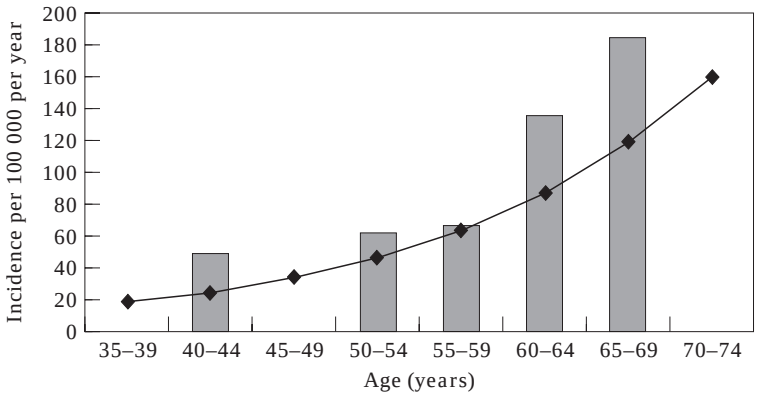
Table 2 Female attenders of the Reykjavik population survey, first visit and disease status of subjects at that time. Women of the Reykjavik Study

Age (years)	30–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	Total
Recognised infarctions	0	0	1	5	16	11	8	9	11	0	61
Unrecognised infarctions	0	0	8	3	10	11	8	1	4	0	45
No infarctions	589	937	1728	2291	2119	1006	488	345	144	20	9667
Total	589	937	1737	2299	2145	1028	504	355	159	20	9773



Age	Incidence	95% CI
35–39	78	(1–428)
40–44	24	(1–133)
45–49	85	(23–216)
50–54	115	(65–187)
55–59	205	(121–321)
60–64	299	(193–430)
65–69	516	(269–856)
70–74	1210	(751–1645)
75–79	1804	(933–2769)
80–84	3050	(1233–5163)

Figure 2 **Incidence of recognised myocardial infarction in women in the Reykjavik Study.**



Unrecogn.	0	1	0	4	4	7	6	0
No infarct	299	494	918	1366	1169	937	542	184
Mean years	3.5	4.2	4.3	4.8	5.2	5.5	6.0	6.2

Figure 3 **Incidence of unrecognised myocardial infarction, in women of the Reykjavík Study; Poisson regression superimposed.**

For a proportional comparison of recognised and unrecognised myocardial infarctions, we evaluated the incidence of recognised infarctions from pairs of visits, relying on information of hospitalization from attenders, in the same manner as with unrecognised events (Table 3). This method excludes fatal events, as well as recognised infarctions among women who did not attend a second time, somewhat lowering the incidence of recognised disease, but offering a realistic comparison of the two forms of the disease. In this manner, unrecognised myocardial infarctions were 33% of all infarctions, with higher rates of incidence in the younger age groups.

There was an age and time trend in the prevalence of recognised myocardial infarction. Thus, for the year 1990 the prevalence was 1·3/1000 population at 35 years. This increased tenfold to age 60 and reached 60/1000 population at 75 years. The prevalence of unrecognised infarctions ranged from 0·9/1000 population at 35 years, increased tenfold to 65 years and was

Table 3 Incidence of recognised and unrecognised myocardial infarctions and the proportion of unrecognised myocardial infarction from the total within pairs of visits. Women of the Reykjavik Study

Age (years)	Recognised non-fatal infarction incidence	Unrecognised infarction incidence	Total incidence non-fatal infarction	Unrecognised infarctions (%)
35–39	27	18	45	40
40–44	40	25	65	38
45–49	59	34	93	36
50–54	87	47	134	35
55–59	128	63	191	33
60–64	188	87	275	31
65–69	276	118	394	30
70–74	405	161	566	28
75–79	596	219	815	27

19·2/1000 population at 75 years (Fig. 4). Out of the total number of infarctions, the proportion of those unrecognised ranged from 41% at 35 years to 24% at 75 years.

There was a significant trend in time for prevalence of recognised infarctions (Fig. 5). Prevalence tripled in all age groups during the study period, adjusted for age, but a time trend could not be established for unrecognised infarctions, possibly due to the small number of cases.

Discussion

In this paper we present the results of a cohort study, with a duration of a quarter of a century, of over 13 000 women. We have determined the prevalence and incidence of myocardial infarction, both recognised and unrecognised, and the changing trends with age and time.

As shown in other epidemiological studies, both forms of disease were strongly age-dependent, the incidence being very low in young women but approximately tripling for every ten years of increasing age. Unrecognised myocardial infarction was demonstrated over repeated visits and shown to be 33% of events presenting between visits. Prevalence increased with age and from 1968–1992 for the recognised form of disease, tripled in all age groups. The prevalence of unrecognised myocardial infarction also showed age dependency but no trend with time.

To determine the disease status of all attenders in the cohort there was an extensive data search in all the Reykjavik hospitals, and information was also sought from local health services for women residing outside Reykjavik. There was a general in-hospital treatment policy for suspected myocardial infarction, with a 50% autopsy rate for all deaths in the early part of the study. The autopsy rate has reduced in more recent cases. Overall 28-day case fatality was 40%, although there is evidence of lower values in younger age groups in Iceland[12].

Health care costs in Iceland are provided through a social security system, in a comparable fashion to that in Scandinavia, and coronary heart disease mortality statistics in Iceland have been shown to be comparable to the other Nordic Countries[10]. During the survey period, ECG coding was subject to quality control as well as retrospective event registration. Loss to follow-up of the study population was minimal.

Incidence

Studies in the U.S.A.[13], Sweden[14–16] Denmark[17,18] and Finland[19] from 1970–1980s showed similar incidence rates of myocardial infarctions for ages 40–64, reported here, although in Finland marked regional variability was reported.

There was more variability in older age groups, and recent publications from Framingham have shown the incidence to be lower than previously published rates, 10–12 per 1000/year for ages 75–94[1,20]. Older results from Copenhagen from the 1970s showed comparable rates for similar ages[17], but more recent results from the Danish MONICA Study show an incidence of 16·7–22·3 per 1000/year for ages 75 to 85+[21]. The increasing rate in Denmark has drawn attention to the high prevalence of smoking among Danish women[22]. Our results, close to recent Danish results, with higher rates in the older age brackets[21], are again consistent with the smoking habits of Icelandic women[22].

Very few studies have the potential to determine the occurrence of unrecognised (silent) myocardial infarction. The incidence of unrecognised myocardial infarction was 41 per 100 000 per year at ages 45–54, reaching 219 per 100 000 at age 75. These are somewhat lower than reported in the Framingham Study, where

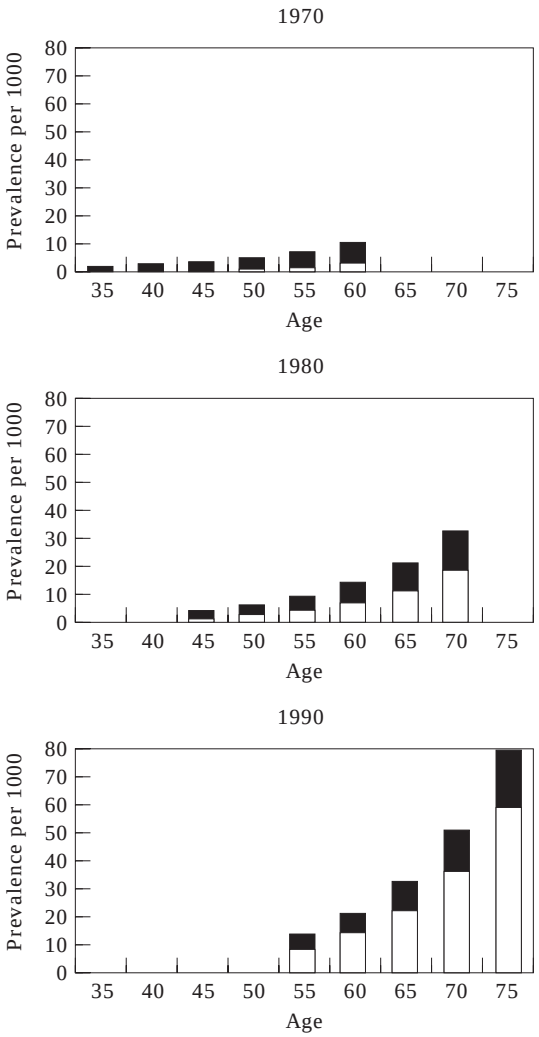


Figure 4 **Prevalence of recognised (□) and unrecognised (■) myocardial infarction and change with calendar time in women of the Reykjavik Study.**

rates were 50 per 100 000 per year at 45–54 reaching 440 at ages 75–84[23]. These differences may result from differences in study design and disease verification, at least in part, since ECG changes of infarction may disappear within a 2-year period[24].

As previously reported[3], the incidence of unrecognised infarctions for men ranged from just below 50 per 100 000 per year at age 45, to a maximum of around 320 cases per 100 000 per year at age 65, but then fell to half that value (150) at age 75. In contrast, among women the incidence rose steadily with age, exceeding that of the men at age 75, with an incidence of 219 per 100 000 per year. Future studies may reveal whether this is an indication of later presentation in women or a fundamentally different pattern.

A methodological difference in disease verification for men and women in the Reykjavik study will affect comparison of numbers, since the data search for men was based on questionnaire information of disease, but for the women was independent of disease status at first visit. This may have resulted in a higher proportion of myocardial infarctions among women being classified as clinically recognised.

The proportional comparison of the incidence of recognised to the incidence of unrecognised infarctions was based on non-fatal events only, and information obtained at repeated visits. With this approach, the proportion of total unrecognised infarctions was 33% for women and can hardly be closer to the previously reported value of 32% for men in the Reykjavik Study. Their rates were higher than previously known and the prognosis was shown to be similar for patients with unrecognised and recognised events[5]. The prognosis for women with unrecognised infarctions has not been determined, but small numbers will set limitations.

The Framingham Study found that 34% of infarctions were unrecognised in women and 26% in men, comparable to our results for women, with higher percentages in younger ages[23,24]. The somewhat higher (40%) proportion of unreported events in the Cardiovascular Health Study for women from 65 to over 85 years may be affected by attendance rates (57%)[25].

Prevalence

Only a few publications in the international literature have addressed the prevalence of myocardial infarction in women. However, in the older age groups, our results are comparable with results from Denmark[26]. In contrast, the prevalence rates in the Reykjavik study are only a half to a third of that shown in older studies for the respective calendar period, especially in the younger age groups[27,28]. A more recent Scottish study also had considerably higher rates than ours in 1990[29]. The prevalence of unrecognised infarctions ranged from 41% of the total in the youngest age groups to 24% in the oldest. The prevalence of recognised myocardial infarctions in Icelandic men was considerably higher than in the women, ranging from a five-fold difference at age 45 down to a two-fold difference at 75 years of age. Women lagged behind the men by 15 years.

Time trends

There is evidence that time and location modify incidence[30–33]. In our cohort, neither the incidence of recognised or unrecognised myocardial infarction showed any change with time. This seems to conflict with the results of declining incidence in the 1980s within population based cross-sectional studies from the MONICA centres in Finland[34] Denmark[35] and Iceland[9,36].

The studies of the MONICA centres, demonstrating a cohort effect of changes within populations and the impact of declining risk factor levels on a population basis, emphasize the influence of population

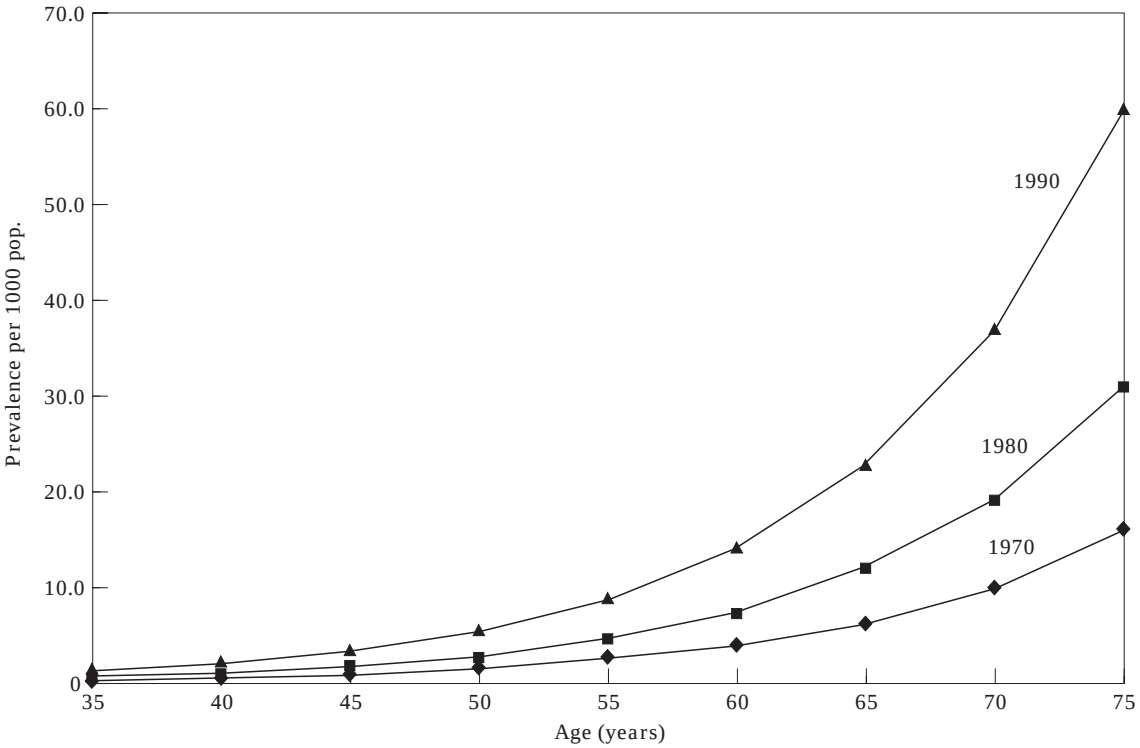


Figure 5 **Prevalence of recognised myocardial infarction in women of the Reykjavik Study as a function of age and calendar year. Logistic regression.**

composition within longitudinal studies. With no trend illustrated within the Framingham Study for 55–64-year-old women in 1953–1983, during a period where many other studies showed increased rates[29], supports this and we also suspect our results to be an example of a period effect.

As previously reported for men, the prevalence of recognised myocardial infarction has been steadily increasing since the onset of the Reykjavik Study in 1967. In 1970, the prevalence of recognised infarctions among women was from 0·6 per 1000 at age 40 to 16 per 1000 at age 75. Respective rates in 1990 were 2·1 and 60. The Framingham Study demonstrated a trend with time from 1953–1973, with an almost four-fold increase in prevalence of myocardial infarctions for women aged 55–64[28].

Limitations of study

With primarily retrospective disease verification, bias may have affected the assessment of the recognised form of the disease, although estimated as prevalence of first visits only. Retrospective verification may have been affected by shifts in diagnostic behaviour and by the increase in awareness by both the public and doctors, affecting referral patterns. However, the diagnostic categories of coronary heart disease within ICD 7–9 were reviewed within a wide range of ischaemic heart disease diagnoses in order to decrease the effect of such changes. In the older material there were more events diagnosed as 'possible', but these did not contribute to the increasing time trends (fewer ECGs recorded and less specific enzyme determinations). Better long-term survival due to improved medical and surgical treatment may explain part of the trend in prevalence, i.e. more patients survived an event during the study. With more sensitive diagnostic methods and increased awareness by doctors and public, smaller infarctions are diagnosed more often, as are some atypical events which previously contributed to unrecognised infarctions. All this adds to the prevalence pool of recognised disease. Although there are possibilities of bias, it is unlikely the effect could be so extensive as to explain a tripling in prevalence. Whether this is due to the natural course of the disease or peri-infarction interventions cannot be decided.

Conclusion

Our results show that age has a strong influence on myocardial infarction. They support previous results showing unrecognised (silent) infarctions to be a third of non-fatal events and relatively as common as in men. The prevalence of recognised myocardial infarction was also low, but age-dependent, with a significant increase in trend, tripling in all age groups during the study period. The prevalence of unrecognised infarctions showed no time trend. The results indicate a need for increased vigilance in diagnosing myocardial infarction, both recognised and unrecognised, in older women at

risk, and emphasize the need for primary and secondary prevention of coronary heart disease in an ageing population.

Approval for the study was granted by the Statistical Licensing Committee and the Statistical Bureau of Iceland.

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